Cardiac resynchronization therapy (CRT) is an established adjunctive treatment for patients with systolic heart failure (HF) and ventricular dyssynchrony. The majority of recipients respond to CRT with improvements in quality of life, New York Heart Association functional class, 6-min walk test, and ventricular function. Management of HF after CRT may include up-titration of neurohormonal blockade and an exercise prescription through cardiac rehabilitation to further improve and sustain clinical outcomes. Diagnostic data provided by the CRT device may help to facilitate and optimize treatment. Initial nonresponder rates remain problematic. We suggest a simple step-by-step management and troubleshooting strategy that integrates device function with advanced HF therapy in patients who do not initially respond to CRT. This algorithm represents a new, comprehensive, collaborative approach between the HF and electrophysiology specialists to further improve and sustain outcomes in the field of CRT. (J Am Coll Cardiol 2005;46:2193–8) © 2005 by the American College of Cardiology Foundation

Approximately 271,000 heart failure (HF) patients in the U.S. have received cardiac resynchronization therapy (CRT) since the Food and Drug Administration approved this therapy in 2001 for moderate to severe HF (1). Indications for CRT are based on the American College of Cardiology, American Heart Association, and Heart Rhythm Society guidelines, which recommend CRT for New York Heart Association functional class III or IV HF patients who are refractory to pharmacologic therapy and have QRS durations ≥130 ms, ejection fractions ≤35%, and left ventricular (LV) end-diastolic dimensions ≥55 mm (level of evidence IIA) (2). These guidelines reflect the results of several large clinical trials that randomized over 2,500 HF patients to CRT versus placebo and demonstrated the benefit of CRT in measurements of functional capacity, exercise tolerance, ventricular remodeling, and reduction in hospitalizations and mortality over a six-month period (3–8).

The beneficial effects of CRT have been shown up to 18 months after device implantation (9). In each of these trials, investigators measured the sole effect of restoring ventricular synchrony on clinical outcomes without significant change in neurohormonal blockade during clinical follow-up. With optimal background medical therapy for HF, about 70% of patients respond to CRT (10).

How best to manage patients after CRT, specifically optimizing medical and other HF therapies, has not been systematically studied. Clinical trials evaluating approaches to the nonresponder and their impact on clinical outcomes are lacking and badly needed. The purpose of this review is to describe and expand upon the management of HF patients after CRT. We discuss optimization and maintenance of pharmacologic therapy along with maintaining adequate device function to improve and sustain clinical outcomes.

**CLINICAL EXPECTATIONS AND MANAGEMENT**

After successful implantation of a CRT device, a series of clinical events can be expected over the next several months. Immediately after implant, assuming adequate LV lead position and thresholds, systolic blood pressure, cardiac output, and stroke work usually increase, whereas end-systolic volumes and pulmonary capillary wedge pressure decrease (11,12). The change in hemodynamic profile is the result of immediate correction of ventricular dyssynchrony resulting in direct improvement of LV systolic dysfunction. Some patients may feel the effects as early as one month after implant though others may require a longer period of time for symptom relief (3). The change in hemodynamic profile (increased cardiac output, systolic blood pressure, and decreased pulmonary capillary wedge pressure) is important to recognize because it may require reduction in...
diuretic dose. From our clinical experience, if a HF patient with near optimal filling pressures receives CRT and has adequate diuresis, failure to reduce diuretics will result in prerenal azotemia which may mask or delay the beneficial effects of CRT.

**Optimization of neurohormonal blockade.** Beta-blockers may also be increased after CRT. Pharmacologic therapy with beta-blockers has dramatically reduced HF mortality, sudden death, and hospitalizations (13–15). Despite these established benefits, use of beta-blockers in recent randomized clinical HF trials is somewhere between 30% and 62% (3,16). Many physicians hesitate starting beta-blocker therapy or increasing beta-blocker dose because of potential worsening HF, hypotension, and bradycardia (17). Cardiac resynchronization therapy improves HF symptoms and blood pressure while restoring synchrony by pacing both ventricles (3,7,11). Therefore, some of the clinical problems for which beta-blocker therapy is abandoned or not aggressively pursued are stabilized with CRT. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial demonstrated that systolic blood pressure increases with CRT and that outcomes of hospitalization and mortality were better with CRT or CRT and defibrillator with concomitant beta-blocker therapy (7).

There are several small retrospective analyses that demonstrate that beta-blocker dose can be increased after CRT (18,19). This is an important observation because approximately 33% to 45% of HF patients in clinical trials of beta-blockers did not achieve maximum target beta-blocker doses (13,17). Furthermore, we have demonstrated that beta-blocker therapy can be re-initiated after CRT in 50% of patients with a history of intolerance to this therapy (19). Cardiac resynchronization therapy is not a replacement for standard pharmacologic therapy, but it may offer the opportunity to augment neurohormonal blockade in patients who have ventricular dysynchrony and current indications for this device. This combination of device therapy and optimal medical management may provide synergistic effects regarding reverse LV remodeling, improved systolic and diastolic function, and increased long-term survival (20–23).

**Cardiac rehabilitation after CRT.** Because improvement in functional capacity can be derived from CRT, an exercise prescription through cardiac rehabilitation may further extend benefits, as noted in other HF populations (24). Although there is a lack of randomized controlled data in the CRT patient (25), the improvements in function provided by CRT may allow a therapeutic opportunity to further increase patients’ functional capacity by cardiac rehabilitation. Although validation of these observations must await completion of the National Heart Lung Blood Institute–sponsored Heart Failure–A Controlled Trial Investigating Outcomes of Exercise Training (HF-Action), these patients may derive additional benefit by continuing to reverse the spiral of functional disability that is often a combination of reduced cardiac function and sedentary behaviors.

**CRT diagnostics for HF management.** Advancement of diagnostics in CRT devices allows clinicians to improve patient care by moving beyond device management to patient management utilities. Devices now have the potential to provide patient-specific clinical information that is useful in the management of heart failure. Trending data such as episodes of atrial fibrillation, ventricular rates during atrial fibrillation, patient activity, and heart rate variability may be used to assess progression of heart failure and efficacy of HF therapies. Decreased heart rate variability is a predictor of death due to progressive heart failure and can be effectively improved by CRT (26,27). Improvement in heart rate variability may be a useful indicator that can be followed by CRT diagnostic information to assess favorable cardiac autonomic profiles and that can affect long-term outcomes. Prospective validated data will be needed to determine how CRT diagnostics can be used and whether or not it can lead to changes in treatment that improve clinical outcomes.

**RESPONDER RATES AND TROUBLESHOOTING CRT DEVICES**

Clinical trials of CRT have demonstrated improvement in functional class, ventricular function, and reverse remodeling while reducing hospitalizations and mortality (3–7,20). However, 30% of patients undergoing CRT appear to derive no benefit from this therapy. This nonresponder rate is derived from several clinical trials in which 30% to 35% of patients showed either no improvement or worsening symptoms after six months of CRT (3,5).

There is no clear consensus or standardized definition of what is considered to be an adequate response to this therapy or when a patient should be considered a nonresponder. Some would consider improvement in NYHA functional class or increased distance walked in 6 min as an adequate response; however, these improvements may be influenced by spontaneous changes as well as by a placebo effect. Indeed, Mehra and Greenberg (28) have suggested that the magnitude of benefit attributable to a surgical device should be determined by evaluating its placebo-subtracted efficacy. For CRT, their analysis indicates that the placebo-subtracted improvement in NYHA functional class is in the realm of 15% to 30% (28). Others would consider changes in oxygen uptake at anaerobic threshold during exercise or reduction of LV systolic and diastolic volumes along with improvement in functional class as an adequate response.
Based on current CRT data, we believe that re-evaluation of a CRT device should be considered if there is no improvement in symptoms after six months of CRT or there is worsening heart failure with increased ventricular remodeling within the first several months after initiation of CRT. Figure 1 represents a potential troubleshooting algorithm for HF patients who are not responding to CRT. This algorithm may or may not improve clinical outcomes and has not been prospectively validated. It does suggest a strategy to manage common problems found in this heart failure population, and it combines that strategy with adequate device optimization and function.

**Clinical problem solving.** A CRT nonresponder should initially be evaluated for prerenal azotemia, development of atrial fibrillation, or cardiac ischemia (in a patient with coronary heart disease). Failure to reduce diuretics in a patient with a functioning CRT device who has achieved optimal filling pressure may result in symptoms that mask the effects of CRT. Rate control up to and including AV node ablation or electrical cardioversion to restore normal sinus rhythm will be necessary in patients who develop atrial fibrillation. Permanent atrial fibrillation in a heart failure patient with CRT will require that the device be reprogrammed from the DDDDR to the VVIR mode in order to prevent tracking of the atria, leading to a rapid ventricular response, and to save battery life. Although one would assume that all attempts at complete revascularization have been pursued in a patient with ischemic cardiomyopathy prior to considering CRT, cardiac ischemia should be reevaluated in a patient not responding to this therapy.

**Device interrogation.** Absence of prerenal azotemia, atrial fibrillation, or cardiac ischemia in a CRT nonresponder should be followed by evaluation and interrogation of the CRT device. Six percent of patients may have LV lead dislodgement during long-term pacing, leading to loss of LV capture (3). Loss of right ventricular (RV) capture also must be evaluated. Comparison of a current electrocardiogram and chest x-ray with a baseline electrocardiogram and chest x-ray from the time of implant may be a simple screening procedure to detect loss of RV or LV capture. Hart et al. evaluated the surface electrocardiographic morphology changes during RV, LV, and BiV pacing in the Post AV Node Ablation Evaluation (PAVE) study population (29). Increment of R-wave and diminution of S-wave amplitude in lead II and/or no change in bundle branch morphology in V1 was associated with loss of RV capture (positive predictive value 93%, negative predictive value 93%). Deepening of S-wave in lead II and/or no change in bundle branch morphology in V1 was associated with loss of LV capture (positive predictive value 71%, negative predictive value 89%). Thus, it may be useful to have a baseline electrocardiogram from the time of implant readily available for comparison with future electrocardiograms to evaluate right and left ventricular capture. This can be confirmed with interrogation of the device.

**Atrioventricular (AV)/interventricular (VV) delay optimization.** Adequate device function in a CRT patient with persistent or worsening symptoms should lead to evaluation of AV and VV delay (if available). Restoration of optimal AV timing may improve systolic performance by optimizing LV preload. In one study, the effect of the AV interval on dp/dt during biventricular pacing or LV free wall pacing was minimal except when it declined to <90 ms (30). In another study, enhancement of dp/dt was observed at AV intervals between 100 and 160 ms with a maximum at 125 ms (31). Even though AV delay has less influence on LV function than CRT pacing site, it should be optimized according to mitral Doppler inflow pattern in someone who is not responding to CRT. An increase in the aortic velocity time integral and a prolongation of the diastolic filling time at the mitral valve by at least 10% to 20% from baseline indicates systolic improvement (32). Kindermann et al. (33) have proposed that the optimal AV delay should provide the longest LV filling time without premature truncation of the A wave by mitral valve closure. Variations of this method have been applied more recently to CRT (34). The sensed AV-delay is programmed to approximately 75% of the PR
interval to ensure complete ventricular pacing. Pulsed-wave Doppler is performed at the tips of the mitral leaflets in the apical four-chamber view to obtain transmitial flow. E and A waves are recorded and the AV delay is shortened by 20 ms until the A-wave is truncated. The truncated A-wave represents early mitral valve closure during ventricular systole. The AV delay is then lengthened by 10 ms until the A-wave is no longer truncated. At this point ventricular contraction should begin just at the end of atrial contraction. There is much discussion regarding the clinical utility of this intervention. The fact that patients with atrial fibrillation and AV node ablation may benefit from CRT suggests that AV interval settings are of less importance in CRT (35). Nevertheless, AV delay should be evaluated in a nonresponder.

There are recent data on VV interval optimization during CRT. During normal electrical activation in patients with normal QRS durations, the delay between RV and LV contraction is about 6 ms (36). New-generation CRT devices allow for optimization of VV delay which, in preliminary studies, has resulted in short-term improvement in hemodynamic measurements of ejection fraction, cardiac output, and increased LV filling times as compared to simultaneous ventricular pacing (37,38). There are no data on long-term clinical outcomes after VV optimization. The optimal VV interval may vary according to etiology of HF. In one study, the optimum VV interval as determined by increase in LV dp/dt in patients with sinus rhythm was 52 ± 31 ms for ischemic cardiomyopathy, 28 ± 30 ms for idiopathic dilated cardiomyopathy, and 37 ± 32 ms for patients with atrial fibrillation (39). Patients with ischemic cardiomyopathy may require longer VV intervals necessitating more pre-excitation of the left ventricle due to the presence of scar tissue resulting in a slower conduction velocity (40).

The optimal pacing sequence may be difficult to predict between patients. In some individuals, CRT with LV pre-activation results in significant cardiac output increase, whereas in other patients improvements have been seen with RV pre-activation as compared to simultaneous CRT (38). The optimal VV interval and sequence of ventricular pre-excitation can be determined by LV filling time as determined by pulsed-wave Doppler transmitial flow (time between onset E wave and the end of the A-wave), cardiac output determined by the LV outflow method, and aortic velocity time integral (38,41). The effects of AV and VV optimization on hemodynamics and ventricular function are immediate (31,38). If inappropriate AV or VV delay is responsible for a lack of response to CRT, optimization of these intervals should translate into improvement of symptoms within a short period of time.

**Echocardiographic dyssynchrony studies.** If there is no improvement in symptoms after device optimization, then noninvasive echocardiographic dyssynchrony studies should be considered. There are several studies suggesting that the presence of interventricular or intraventricular dyssynchrony detected by a different echocardiographic technique prior to CRT implant is the best predictor of improvement of LV function and reverse remodeling after CRT (42–46). Specifically, septal to posterior wall motion delay ≥130 ms as measured by M-mode echocardiography at the level of papillary muscle (42), interventricular mechanical delay ≥ 40 ms defined as the time difference between LV and RV pre-ejection intervals (43), and interventricular dyssynchrony ≥65 ms as detected by tissue Doppler imaging (44) are significant measurements of dyssynchrony and predict response to CRT. After successful CRT there should be minimal interventricular or intraventricular dyssynchrony. Yu et al. (47), using tissue Doppler imaging, showed complete resolution of interventricular dyssynchrony after CRT. Pirzalis et al. (42) report substantial reduction of intraventricular dyssynchrony with a significant reduction of septal to posterior wall motion delay. If significant interventricular or intraventricular dyssynchrony is still present in a CRT nonresponder, then lead position or revision should be considered through transvenous or epicardial lead placement. The implant should attempt to pace the most delayed sites of the left ventricle as detected by echocardiography to maximize the effect of CRT. Optimal resynchronization in the region with the latest activity detected through echocardiographic parameters leads to improved clinical response in CRT patients (48).

**Evaluation of mitral regurgitation.** Persistent symptoms despite correction of ventricular dyssynchrony should be followed by evaluation for significant mitral regurgitation. Causes of functional mitral regurgitation (MR) in dilated cardiomyopathy range from ventricular dilation with increasing distance between papillary muscles and the enlarged mitral annulus restricting leaflet motion, to delayed activation of the posteromedial papillary muscle resulting from ventricular dyssynchrony. Functional MR is reduced by CRT (49). Persistent MR despite correction of ventricular dyssynchrony may mask the effects of CRT. Recent studies have shown that mitral valve surgery offers symptomatic improvement to MR patients with poor LV function (50,51). In selected patients, mitral valve surgery should be considered to correct persistent significant MR in a CRT nonresponder.

An HF patient with CRT who persists with symptoms despite adequate device function and absence of dyssynchrony or significant MR should be considered a true nonresponder. Most patients studied in CRT clinical trials have NYHA functional class III heart failure. There is a growing enthusiasm for the use of cardiac support devices in this patient population, including CRT nonresponders (52,53). In selected nonresponders who progress to NYHA functional class IV heart failure, the use of LV assist devices or cardiac transplantation should be considered (54,55).

**CONCLUSIONS**

Cardiac resynchronization therapy is now considered for severe heart failure refractory to pharmacologic therapy in
patients with prolonged QRS intervals. As the number of patients receiving CRT continues to grow, a new, more uniform approach between heart failure and electrophysiologist specialists will be needed to maintain and improve clinical results that are achievable through this therapy (56). This standardized approach will need to address issues of patient selection, changes in pharmacology after CRT, and maintenance of adequate CRT device function. It is the combination of these three factors that will further improve outcomes in the field of CRT.

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Aranza, Jr. et al. 2197

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